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EXAMINER	
FOSTER, CHRISTINE E	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/519,738	SYMONDS, WILLIAM HUNTER	
	Examiner	Art Unit	
	Christine Foster	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 July 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8 and 10-20* is/are pending in the application.

4a) Of the above claim(s) *14-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8 and 10-13* is/are rejected.

7)☒ Claim(s) *1* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/28/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I, claims 1-8 and 10-13 in the reply filed on 7/30/07 is acknowledged. The traversal is on the ground(s) that there is a corresponding special technical feature of Groups I, II and II, namely, "alkaline conditions sufficient to release the moieties from the beads" (Reply, page 2, the second paragraph).

This is not found persuasive because Hixson et al. teach an alkaline solution of 0.25 M NaOH as noted in the previous Office action on page 3, the first paragraph.

Applicant also points to the specific pH range of pH 12.5 to 13.5 in relation to the technical feature of alkaline conditions. Applicant also mentions that the alkaline conditions should not extract inorganic iron from the beads. However, the specific pH range of pH 12.5 to 13.5 is not recited in independent claims 1 or 19. Similarly, the feature that the alkaline conditions should not extract inorganic iron from the beads is not recited in claim 1. Such remarks are therefore not persuasive because a determination of unity of invention is made *only in relation to the independent claims* in an international application and not the dependent claims (see MPEP 1801).

Furthermore, the Examiner notes that the alkaline solution of 0.25 M NaOH taught by Hixson et al. has a pH of 13.4[1], and therefore would also read on the specific pH range to which Applicant points.

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[1] The pH of a 0.25 M NaOH solution may be calculated according to the Henderson-Hasslebalch equation as follows:
$[H+][OH^-] = 1.0 \times 10^{-14}$
$[H+][0.25] = 1.0 \times 10^{-14}$
such that $[H^+] = 4 \times 10^{-14}$
$pH = -\log [H^+] = -\log[4 \times 10^{-14}] = 13.4$

Therefore, the technical feature of "alkaline conditions sufficient to release the moieties from the beads" does not represent a special technical feature since it does not make a contribution over the prior art.

Applicant further argues that the method steps of Groups I and III may be considered a corresponding technical feature linking these two inventions since the claims of these inventions differ only with respect to whether the analyte contains or is labeled with a heme moiety (Reply, page 2, the third paragraph). This is not found persuasive since under PCT Rule 13, determination of unity of invention is made as a whole by considering all of the claimed inventions in the application and not by comparing individual subsets of claims. See MPEP 1850, the section 13.2 in particular.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 14-20 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 7/30/07. Claims 1-8 and 10-13 are subject to examination below.

Manner of Making Amendments under 37 CFR 1.121

3. In the interest of expediting prosecution, Applicant's preliminary amendment of 12/28/04 has been accepted. However, Applicant is reminded of the proper format for amendments to the claims. Specifically, it is noted that the amendments to claims 4 and 11 are non-compliant because quotation marks (" ") have apparently been used to indicate deleted subject matter from

the claim, which is improper. The text of any deleted matter must be shown by strike-through except that double brackets placed before and after the deleted characters may be used to show deletion of five or fewer consecutive characters. See MPEP 714.

Information Disclosure Statement

4. Applicant's Information Disclosure Statement filed **2/28/05** has been received and entered into the application. The references therein have been considered by the examiner as indicated on the attached form PTO-1449.

5. The reference "**Abstract of Japanese Patent Document No. 07140143, June 2, 1995**" cited in the Search Report mailed 9/30/03 and referred to in Applicant's letter accompanying the IDS of 2/28/05 has been considered, but will not be listed on any patent resulting from this application because it was not provided on a separate list in compliance with 37 CFR 1.98(a)(1). In order to have the references printed on such resulting patent, a separate listing, preferably on a PTO/SB/08A and 08B form, must be filed within the set period for reply to this Office action.

6. Applicant is reminded that the listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Claim Objections

7. Claim 1 is objected to because of the following informalities:

8. Claim 1 recites that "haem moieties" are released from the beads in step (c) and subsequently detected in step (d). However, there is no explicit connection in the claim between the "haem moieties" and the analyte that is being detected. Applicant is requested to clarify that the "haem moieties" referred to in steps (c)-(d) are those that are contained within the analyte.

9. In addition, the language "**the** released haem moieties" is suggested in step (d) in order to make clear that the haem moieties detected are those which were released in the previous step.

10. There appears to be an extra space in step (b) between word "sample" and the comma that follows.

Claim Rejections - 35 USC § 112

11. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

12. Claims 1-8 and 10-13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

13. Claims 1-8 and 10-13 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: an active method step in which the analyte is detected.

The preamble of independent claim 1 recites "[a] method for detecting an analyte". The claim concludes with the step of "detecting released haem moieties". However, there is no recited step in which the method objective of detecting *an analyte* is actually accomplished. Alternatively, a correlation step may be recited describing how the results of the assay relate back to the method objective as recited in the preamble.

Claim Rejections - 35 USC § 103

14. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

15. Claims 1-3, 5, 8, and 10-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ewetz et al. ("Factors Affecting the Specificity of the Luminol Reaction with Hematin Compounds" Anal Biochem. 1976 Apr;71(2):564-70, Applicant's IDS of 2/28/05) in view of Hixson et al. (WO 98/54578, Applicant's IDS).

Ewetz et al. teach a procedure for the assay of heme-containing enzymes and heme-containing proteins ("hematin enzymes" and "hematin compounds") by a luminol-based chemiluminescence assay (see in particular the abstract; page 564 to page 565, the first full paragraph; and pages 566-567, "Results").

The assay involves subjecting the sample containing the heme-containing compound to be assayed with 0.1 M NaOH before addition of alkaline luminol reagent (see the abstract and page 566, "Luminol Assay Procedure". This NaOH incubation results in an increase of the

specificity and sensitivity of the luminol reaction with the heme moieties ("protoporphyrin compounds").

The alkaline conditions taught by Ewetz et al. involving 0.1 M NaOH are "sufficient to release haem moieties" from beads as claimed since the instant specification indicates that such conditions include alkaline pH values in the range of pH 12.5-13.5 (specification, page 3); 0.1 M NaOH has a pH value of pH 13[2].

The reference differs from the instantly claimed invention in that it fails to specifically teach an assay involving magnetic beads having specific binding partners for the heme-containing enzymes and proteins, and further fails to teach magnetic separation. In other words, the assay of Ewetz et al. is performed directly on the sample without any preliminary separation steps.

Hixson et al. also teach chemiluminescent methods for the detection of hemoglobin. The reference teaches that a portion of hemoglobin is normally glycosylated, and that the amount and/or proportion of glycosylated hemoglobin is an indicator of the presence or absence of diabetes (pages 1-2).

To distinguish between the different fractions of hemoglobin in a single sample, the fractions are first separated by chemical or physical means before the chemiluminescent reaction is induced (page 2, lines 18-35). For example, a binding agent selective for one of the hemoglobin forms may be bonded to a solid phase, followed by separation of the solid and liquid

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[2] pH of a 0.1 M NaOH solution:
$[H+][OH^-] = 1.0 \times 10^{-14}$
$[H+][0.1] = 1.0 \times 10^{-14}$
such that $[H^+] = 1 \times 10^{-13}$
$pH = -\log [H^+] = -\log[1 \times 10^{-14}] = 13$

phases from each other. More particularly, dihydroxyboryl compound can be immobilized on a solid support in order to selectively separate glycosylated hemoglobin (page 5, lines 14-25).

Solid phases include paramagnetic particles, which are amenable to automated assays (page 6, line 15 to column 7, line 4).

Therefore, it would have been obvious to one of ordinary skill in the art to perform a preliminary separation step, as taught by Hixson et al., prior to the chemiluminescence reaction of Ewetz et al. Specifically, it would have been obvious to specifically isolate the glycated fraction of hemoglobin from the sample using magnetic beads having glycated hemoglobin-specific ligands immobilized thereon. One would be motivated to do this in order to specifically detect the glycated form of hemoglobin, which is an indicator of diabetes.

With respect to claim 3, Hixson et al. teach washing of the paramagnetic particles after magnetic separation, wherein the beads would necessarily be resuspended in the wash solution (see the paragraph bridging pages 6-7; Example 2) and also exemplify detection without an intervening separation step (Examples 1-2). Therefore, it would have been obvious to resuspend the beads in a washing solution prior to detection by the method of Ewetz et al. as exemplified by Hixson et al. Similarly, it would have been obvious to directly detect chemiluminescence without an intervening separation step as exemplified by Ewetz et al., and also for the benefit of reducing assay steps, simplifying the assay and reducing time.

With respect to claim 5, Hixson et al. teach that the magnetic particles are washed after magnetic separation and prior to detection, wherein the beads would necessarily be resuspended in the wash solution in the course of washing (see the paragraph bridging pages 6-7; Example 2).

With respect to claim 8, the alkaline conditions taught by Ewetz et al. involving 0.1 M NaOH (pH 13) would be "sufficient to release haem moieties without extracting inorganic iron from the beads" since this falls within the range of pH 12.5-13.5 that is disclosed in the instant specification as constituting suitable conditions for this purpose (specification, page 3).

With respect to claims 10 and 12, the luminol detection method of Ewetz et al. involves initial addition of luminol reagent followed by oxidant (sodium perborate) (see page 565, "Reagents"; page 566, "Luminol Assay Procedure"; and Figure 2 and legend). The amount used would necessarily be sufficient to generate a signal, since light emission was observed (Figure 2 and legend).

With respect to claim 11, although Ewetz et al. do not specifically teach that the amount of perborate is sufficient to oxidize all of the luminol, absent evidence of criticality it would have been obvious to one of ordinary skill in the art to discover the optimum or workable ranges out of the course of routine optimization. See MPEP 2144.05.

16. Claim 4 is rejected under 35 U.S.C. 103(a) as being unpatentable over Ewetz et al. in view of Hixson et al. as applied to claim 1 above, and further in view of Valkirs et al. (US 6,503,722 B1).

Ewetz et al. and Hixson et al. are as discussed above. Hixson et al. teaches a wash step (where the beads would necessarily be resuspended in the wash solution during the course of washing), but fails to teach separating the beads from the suspension after step (c) and performing detection on the separated suspension.

Valkirs et al. teaches a magnetic bead-based assay for detection of an analyte (C. *difficule* toxin A), in which after the magnetic separation is completed, the magnetic beads are dissociated and removed from the solution in order to obtain a highly concentrated preparation of the analyte (the abstract). This makes possible a very sensitive assay since the effect of nonspecific binding to the beads is eliminated, allowing a greater amount of beads to be used in the assay so that all of the analyte present in the sample can be captured (ibid and column 20, line 32 to column 21, line 25; and especially at column 21, lines 10-17).

Therefore, it would have been obvious to one of ordinary skill in the art to remove the magnetic beads from the solution after magnetic separation in the method of Ewetz et al. and Hixson et al. and to perform the detection method on the bead-free suspension as taught by Valkirs et al. One would be motivated to do this in order to reduce the effect of nonspecific binding, allowing more beads to be used so that all of the glycated hemoglobin in the sample could be captured on the beads, thus increasing the assay sensitivity.

17. Claim 13 is rejected under 35 U.S.C. 103(a) as being unpatentable over Ewetz et al. in view of Hixson et al. as applied to claim 1 above, and further in view of Wang et al. (US 5,431,793).

Ewetz et al. and Hixson et al. are as discussed above. Hixson et al. teaches boronic acid ligands that are immobilized on the solid phase for selectively isolating glycated hemoglobin. However, the reference fails to specifically teach immobilized ligands for glycated hemoglobin that are *antibodies or binding fragments thereof.*

Wang et al. teach methods for measuring glycated hemoglobin in a sample, and in particular the amount of the Hb A1c form of glycated hemoglobin (column 1, line 19 to column 2, line 3). The amount of Hb A1c in blood is related to time-averaged glucose concentration, thereby providing a way of assessing the control of diabetes (column 1, lines 55-63; column 7, lines 20-37). Wang et al. teach that the Hb A1c form can be determined in a sample containing other forms of hemoglobin using an antibody that specifically binds this form (column 3, lines 40-65). Antigen binding fragments are also contemplated (column 6, lines 42-44).

Therefore, it would have been obvious to one of ordinary skill in the art to substitute the antibody or binding fragment thereof that is specific for glycated hemoglobin of Wang et al. for the boronic acid ligands of Hixson et al. One would be motivated to do this based on the art-recognized suitability of anti-Hb A1c antibodies for the purpose of specifically binding glycated hemoglobin, which is the same purpose for which the boronic acid ligands are employed by Hixson et al.

18. Claims 1-2, 4, 6-8, and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bruno et al. ("Immunomagnetic-Electrochemiluminescent Detection of Bacillus anthracis Spores in Soil Matrices" Appl Environ Microbiol. 1996 Sep;62(9):3474-3476) in view of Valkirs et al., Giaever et al. (US 3,970,518) and Heroux et al. (US 2002/0146722 A1).

Bruno et al. teach methods for detecting *Bacillus anthracis* spores, which contain heme as indicated in the present application (see, e.g., claim 7), comprising the steps of (a) contacting soil suspensions with magnetic beads having immobilized thereon Gt 578 capture antiserum specific for *B. anthracis* spores; (b) separating the beads from the sample by immunomagnetic

separation; and (d) detecting the analyte by electrochemiluminescence (ECL) assay (see especially the abstract and page 3474). The ECL assay employs a ruthenium(II) trisbipyridine-based label (see page 3474, the paragraph bridging the right and left columns to right column, second paragraph).

The teachings of Bruno et al. differ from the instantly claimed invention in that the reference fails to specifically teach (c) subjecting the beads to alkaline conditions sufficient to release heme moieties from the beads. The reference also teaches electrochemiluminescence assay using a ruthenium(II) trisbipyridine-based label but fails to specifically teach an assay that employs luminol.

Valkirs et al. is as discussed above, which teaches a magnetic bead-based assay for detection of an analyte (C. *difficule* toxin A), in which after the magnetic separation is completed, the magnetic beads are dissociated and removed from the solution in order to obtain a highly concentrated preparation of the analyte (the abstract). This makes possible a very sensitive assay since the effect of nonspecific binding to the beads is eliminated, allowing a greater amount of beads to be used in the assay so that all of the analyte present in the sample can be captured (ibid and column 20, line 32 to column 21, line 25; and especially at column 21, lines 10-17).

Giaever et al. also relates to immunomagnetic separation methods, in which bacteria and other analytes can be captured on antibody-bearing magnetic particles (see especially column 1, lines 35-55 and column 2, line 8 to column 3, line 20). The reference teaches that following the capture, separation, and wash steps, the captured analytes may be cleaved from the magnetic

particles by use of a cleaving agent (column 2, line 66 to column 3, line 20). Suitable cleaving agents are alkaline solutions of pH 9-13 (column 3, lines 14-18).

In light of the teachings of Valkirs et al., it would have been obvious to one of ordinary skill in the art to perform a dissociation step to remove the magnetic beads from the captured spores in the method of Bruno et al. prior to ECL detection, so as to allow increased sensitivity in the assay. In dissociating the captured spores, the heme moieties contained therein would also necessarily be released as well.

It would have been further obvious to select known means of dissociating captured analytes from magnetic beads when performing this dissociation step. In particular, it would have been obvious to subject the magnetic beads to alkaline solutions of pH 9-13 as taught by Giaever et al., based on their art-recognized suitability for this same purpose.

Heroux et al. teach electrochemiluminescent (ECL) labels, including both ruthenium(II) trisbipyridine-based labels (as taught in Bruno et al.) and luminol [0048]. Therefore, although Bruno et al. exemplify the use of $Ru(bpy)_3^{2+}$ as the ECL label, it would have been obvious to substitute luminol as the ECL label based on its art-recognized suitability for the same purpose.

Conclusion

19. Claims 1-8 and 10-13 are rejected.

20. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Muller-Schulte et al. (US 6,204,033 B1) is largely cumulative to the teachings of Hixson et al. discussed above, teaching methods for quantitative detection of glycated hemoglobin by

magnetic bead separation technology (see in particular the abstract; column 8, lines 18-63; and Example 26). The reference teaches that glycated hemoglobin can then be analyzed photometrically using known analysis processes, but fails to specifically exemplify luminol-based chemiluminescence analysis. By immobilizing boronic acid ligands as specific binding partners (column 8, lines 18-63; and Example 26).

Olsson et al. ("Chemiluminescent immunosorbent assay of serum myoglobin based on the luminol reaction" Clin Chim Acta. 1984 Mar 27;138(1):31-40) and Olsson et al. ("A sensitive method for determination of serum hemoglobin based on iso-luminol chemiluminescence" Clin Chim Acta. 1982 Jul 1;122(2):125-33) teach assays for heme-containing proteins using luminol or iso-luminol chemiluminescence. The Olsson et al. 1984 reference also involves initial separation on a solid phase (polystyrene tubes).

Takashi et al. (Patent Abstracts of Japan, Publication No. 04-324358, published 11/13/1992, abstract translation attached) teaches a method of measuring human hemoglobin in feces, using a solid phase (which may be a bead) having immobilized thereon an anti-human Hb antibody, followed by luminol-generated chemiluminescence. However, the reference does not specifically teach *magnetic* beads, or subjecting the beads to alkaline conditions sufficient to release heme moieties from the beads.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christine Foster whose telephone number is (571) 272-8786. The examiner can normally be reached on M-F 8:30-5. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached at (571) 272-0823. The fax

phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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